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Biochemical correlates of depression and cognitive impairment: role of vitamin D, vitamin B12, and homocysteine

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Abstract

Background: Depression is frequently accompanied by cognitive dysfunction, both of which may be influenced by biochemical disturbances involving Vitamin D, Vitamin B12, and homocysteine. Deficiencies in these micronutrients have been linked to impaired neurotransmission and neuroplasticity. **Aim:** To evaluate serum Vitamin D, Vitamin B12, and homocysteine levels in patients with depression and cognitive dysfunction and to assess their correlation with psychometric scores.

Methods: A prospective observational study was conducted at Viswabharathi Medical College, Kurnool**,** from April 2024 to June 2025**.** Sixty patients with Major Depressive Disorder (DSM-5 criteria) and sixty age- and sex-matched healthy controls were evaluated. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D)**,** and cognitive function was measured using MMSE and MoCA**.** Serum Vitamin D, Vitamin B12, and homocysteine levels were estimated using chemiluminescent and enzymatic assays. Statistical analysis was performed using SPSS v26.0, with $p < 0.05$ considered significant.

Results: Depressed patients had significantly lower Vitamin D and B12 levels and higher homocysteine levels compared to controls ($p < 0.001$). Cognitive scores (MMSE, MoCA) negatively correlated with HAM-D and homocysteine but positively with Vitamin D and B12.

Conclusion: Micronutrient deficiencies and elevated homocysteine are strongly associated with depression severity and cognitive decline, suggesting potential benefit from biochemical screening and nutritional intervention.

Key Words: Depression, Cognitive dysfunction, Vitamin D, Vitamin B12, Homocysteine

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Introduction

Depression and cognitive dysfunction often co-exist and represent a significant clinical burden in psychiatry and neuroscience [1]. Emerging evidence suggests that micronutrient status and one-carbon metabolism may play a mechanistic role in these disorders. In particular, low serum levels of 25-hydroxyvitamin D (vitamin D) have been reported in individuals with major depressive disorder, and associations with poorer cognitive performance have also been observed [2, 3]. Likewise, vitamin B12 deficiency and elevated homocysteine (Hcy) concentrations are recognised risk factors for neurocognitive impairment and have been implicated in mood disorders [4]. Taken together, these biochemical variables provide a promising intersection of psychiatry and biochemistry, offering a model for exploring how nutritional and metabolic perturbations contribute to both affective symptoms and cognitive decline. The aim of the present study is to evaluate the serum concentrations of vitamin D, vitamin B12 and homocysteine in patients diagnosed with depression with or without cognitive complaints and to examine their correlation with cognitive dysfunction using standardized neuropsychological measures.

Methods:

This prospective observational study was conducted in the department of Psychiatry and department of Biochemistry, Viswabharathi Medical College, Kurnool, from April 2024 to June 2025**.** Ethical approval for the study was obtained from the Institutional Ethics Committee, and all participants provided written informed consent before enrolment. Patients aged between 18 and 60 years, clinically diagnosed with Major Depressive Disorder (MDD) according to the DSM-5 criteria, were recruited from the psychiatry outpatient and inpatient departments as test group; simultaneously equal number of normal individuals were also recruited as control. Those with comorbid neurological disorders, substance dependence, chronic renal or hepatic disease, and those on vitamin or folate supplementation were excluded

Each participant underwent a detailed clinical and psychiatric evaluation. The severity of depression was assessed using the Hamilton Depression Rating Scale (HAM-D)**,** and cognitive function was measured using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment

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(MoCA) tools [5]. A control group of age- and sex-matched healthy individuals without psychiatric illness or cognitive complaints was also included for comparison. Demographic data, medical history, dietary patterns, and sunlight exposure duration were recorded using a pre-tested structured proforma.

Venous blood samples (5 mL) were collected in the morning after overnight fasting under aseptic precautions for biochemical analysis. Serum was separated by centrifugation and stored at −20 °C until analysis. Serum 25-hydroxyvitamin D**,** Vitamin B12 and homocysteine concentrations were estimated as per the institutional protocol. Internal and external quality controls were applied to ensure analytical accuracy.

Statistical analysis was conducted using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Differences between groups were analyzed using the Student's t-test or Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables. Correlations between biochemical parameters and depression severity or cognitive scores were examined using Pearson's or Spearman's correlation coefficients. A p-value < 0.05 was considered statistically significant.

Results:

A total of 120 participants were enrolled, 60 patients with clinically diagnosed depression and 60 healthy controls matched for age and gender. The mean age of the study population was 41.3 ± 10.2 years, with a female predominance in both groups. Baseline body mass index and demographic variables did not differ significantly between the groups (Table 1). Serum biochemical analysis revealed significantly lower mean Vitamin D and Vitamin B12 levels in depressed patients compared to controls, while mean homocysteine levels were markedly elevated ($p < 0.001$) (Table 2). Cognitive performance assessed using MMSE and MoCA demonstrated reduced scores among depressed patients, indicating mild cognitive impairment associated with the disorder. The mean HAM-D score in the patient group confirmed moderate to severe depression severity (Table 3). Correlation analysis demonstrated a positive relationship between serum Vitamin D and Vitamin B12 levels with cognitive test scores (MMSE, MoCA) and a negative correlation with HAM-D depression scores, suggesting that micronutrient deficiency contributed to poorer cognitive and mood outcomes. Conversely, homocysteine levels exhibited a significant inverse correlation with cognitive scores and a positive correlation with depression severity ($r = 0.51$, $p < 0.01$) (Table 4).

Discussion:

In the present study, Table 1 shows that the depressed patient and control groups were well matched with respect to age and gender, thereby reducing confounding due to demographic imbalance. This is important because age and sex differences can influence both micronutrient status and depressive symptomatology: for example, low serum vitamin D levels have been shown to be associated with depressive symptoms irrespective of age or gender in obese adults, reinforcing the validity of matching these variables. [6] Gender-specific analyses also hint at differential micronutrient associations one large population study found that deficiencies of B vitamins, including vitamin B12, had stronger associations with depressive symptoms in females than males. [7] Moreover, demographic characteristics such as BMI and sun-exposure time (though not shown in Table 1) may interrelate with age and gender in determining serum vitamin D and B12 levels. This matching therefore enhances internal validity of our biochemical comparisons. By ensuring that age and sex distributions were similar between groups, the observed differences in vitamin D, vitamin B12, and homocysteine levels are less likely to be artefacts of demographic disparity, thereby strengthening the inference that differences reflect biochemical–psychiatric association rather than simple demographic confounding.

The findings presented in Table 2 reveal significantly lower serum concentrations of 25-hydroxyvitamin D and vitamin B12 accompanied by elevated homocysteine levels in the depressed cohort compared with controls. These biochemical abnormalities are consistent with mounting evidence that micronutrient deficiencies and altered one-carbon metabolism contribute to mood disorders and cognitive impairment. For example, a dose–response meta-analysis demonstrated that each 10 ng/mL increment in serum 25-hydroxyvitamin D was associated with a 12% lower risk of incident depression in older adults [8]. Similarly, systematic review data implicate vitamin B12 deficiency in poorer cognitive performance and depressive symptoms, with meta-analytic effect sizes showing strong associations between low B12 and both domains [9]. Elevated homocysteine, as another biochemical marker, has been repeatedly linked to cognitive decline and mood disorder pathology through mechanisms involving neurotoxicity, vascular injury and impaired methylation capacity [10].

Together, these observations bolster the biological plausibility of our results: depressed patients not only had lower vitamin D and B12 levels but also higher homocysteine levels, suggesting convergent pathways of depleted neuro-nutrients and disrupted methylation. The biochemical derangements may

reflect nutritional inadequacy, malabsorption, behavioural changes (e.g., reduced sunlight exposure, altered diet) or disease-related metabolism shifts. Since our groups were matched for age and gender, the biochemical differences are less likely to stem from demographic confounders and more likely to reflect disease-linked or risk-linked metabolic perturbations. Clinically, the findings point toward the value of screening for these nutritional and metabolic biomarkers in depression, and raise the possibility that corrective supplementation might influence cognitive and mood outcomes though causality remains to be firmly established.

Table 3 of our study demonstrates that participants with depression had significantly lower scores on both the MMSE and the MoCA compared to normal cut-offs, while their HAM-D scores confirmed moderate to severe depressive symptoms. These findings align with accumulating evidence that cognitive dysfunction accompanies mood disorders: for instance, one study found that cognitive impairment increased as depression severity grew, with MMSE scores falling in proportion to HAM-D findings [11, 12]. Another cross-sectional cluster analysis in older adults with depression demonstrated negative correlations between MMSE totals and biomarker levels reflecting neuroaxonal injury, reinforcing that more severe depression often co-exists with poorer cognitive functioning [13]. A recent investigation of cognitive screening among depressed patients found that while MoCA may be less sensitive to distinguishing depression-related cognitive change alone, the degree of cognitive impairment still tracked with depression severity [13]. In our sample, the inverse relationship between HAM-D and both MMSE/MoCA suggests that as mood symptoms intensified, cognitive performance declined—supporting the concept of a "dual burden" of affective and cognitive dysfunction in depression. Clinically, this underscores the importance of incorporating brief cognitive assessments in depressive illness management, as poorer cognition may amplify disability, reduce treatment response, and foreshadow adverse longer-term outcomes.

The findings in Table 4 showing significant correlations between serum biochemical markers (vitamin D, vitamin B12, homocysteine) and psychometric scores (MMSE, MoCA, HAM-D)—are consistent with emerging evidence of the intertwined roles of micronutrient status and one-carbon metabolism in mood and cognitive disorders. For instance, in a cohort of children and adolescents with depression, lower levels of vitamin B12 and vitamin D and higher homocysteine were all significantly associated with increased depression severity [14]. Furthermore, a recent large study found that lower B-vitamin levels (including B12) were positively associated with both depressive symptoms and cognitive dysfunction in adults [15]. In parallel, elevated homocysteine has been implicated as a risk factor for both depression and cognitive impairment in several adult samples [16].

Taken together, our observed strong positive correlation between vitamin D/B12 and cognitive scores (MMSE, MoCA) and the negative association between these vitamins and HAM-D scores lends biological plausibility: diminished neuro-nutrient support may impair neuroplasticity, while elevated homocysteine may reflect vascular and methylation-related neurotoxicity. Clinically, this underscores the potential utility of combined biochemical screening and psychometric assessment in depressed patients with cognitive complaints; the significant correlations suggest these biomarkers may help stratify risk of cognitive decline. However, while the cross-sectional correlations are robust, they do not prove causation—interventional trials will be needed to clarify whether correcting these biochemical deficits leads to improvements in cognition or mood.

Conclusion: This prospective study demonstrated a clear biochemical association between depression and altered levels of Vitamin D, Vitamin B12, and homocysteine. Patients with depression exhibited significantly reduced serum Vitamin D and B12 concentrations and elevated homocysteine levels, which correlated with increased depression severity and poorer cognitive performance. These findings highlight the interplay between micronutrient deficiencies, one-carbon metabolism, and neuropsychiatric dysfunction. Routine screening and correction of these biochemical abnormalities may serve as an adjunctive strategy in managing depression and cognitive impairment. Future longitudinal and interventional studies are warranted to determine causal relationships and therapeutic efficacy of micronutrient supplementation.

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Table 1: Baseline characteristics of the study participants

Parameter	Test	Control	p-value
Age	41.8 ± 10.6	40.9 ± 9.8	0.62
Gender (M/F)	24/36	26/34	0.74
BMI (kg/m²)	23.6 ± 2.9	23.2 ± 3.1	0.48

Table 2: Biochemical parameters in the study groups

Parameter	Test	Control	p-value
Vitamin D	18.9 ± 6.2	27.4 ± 7.8	<0.001
Vitamin B12	248 ± 82	342 ± 91	0.002
Homocysteine	18.2 ± 5.3	10.4 ± 3.1	<0.001
* (ng/mL); **pg/mL; ***µmol/L			

Table 3: Cognitive scores and depression severity among the study members

Parameter	Mean ± SD	Normal range	p-value
MMSE Score	23.1 ± 2.8	≥ 27	<0.001
MoCA Score	21.9 ± 3.1	≥ 26	<0.001
HAM-D Score	22.8 ± 4.6	≤ 7	<0.001

Table 4: Correlation between Biochemical parameters and psychometric scores

Variable	MMSE (r)	MoCA (r)	HAM-D (r)	p-value
Vitamin D	0.48	0.44	−0.52	<0.01
Vitamin B12	0.41	0.39	−0.47	<0.01
Homocysteine	−0.45	−0.49	0.51	<0.01